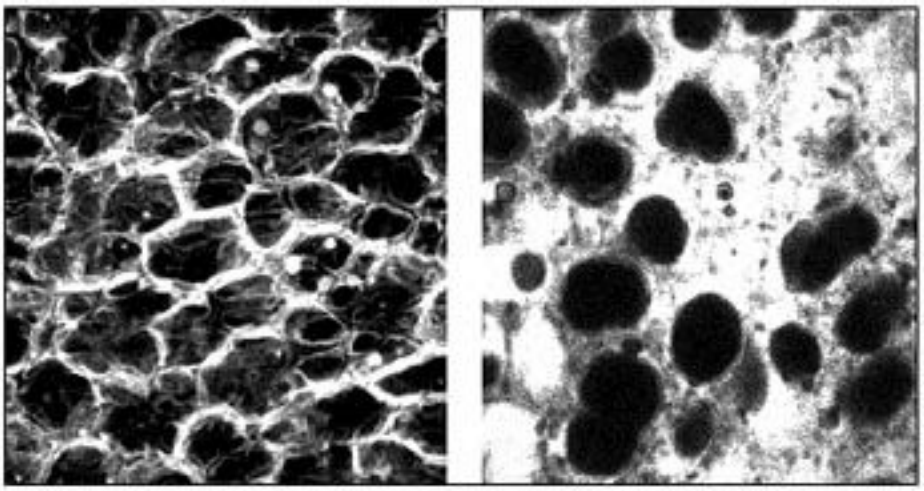
Respiratory Diseases



Laser confocal images of subpleural alveoli of a normal (left) and an edematous, or flooded (right) rat lung. The edema fluid appears white, the alveolar walls gray and airpockets are black. (Gajic and Lee, unpublished). (Reproduced from the web site of Rolf D Hubmayr, M.D., Mayo Clinic and Foundation, Rochester, MN, with permission.)

The respiratory system plays a vital role in delivering oxygen to the body — fuel for all the body's functions. It also removes carbon dioxide waste, eliminates toxic waste, regulates temperature, and stabilizes blood acid-alkaline balance (pH).

The lungs are the largest part of the respiratory system and have both "respiratory" and "non-respiratory" functions. The respiratory function involves gas exchange — the transfer of oxygen from the air into the blood and the removal of carbon dioxide from the blood. Non-respiratory lung functions are mechanical, biochemical, and physiological. The lungs provide a defense against bacterial, viral and other infectious agents; remove various metabolic waste products; control the flow of water, ions, and large proteins across its cellular structures; and manufacture a variety of essential hormones and chemical agents that have important biological roles.

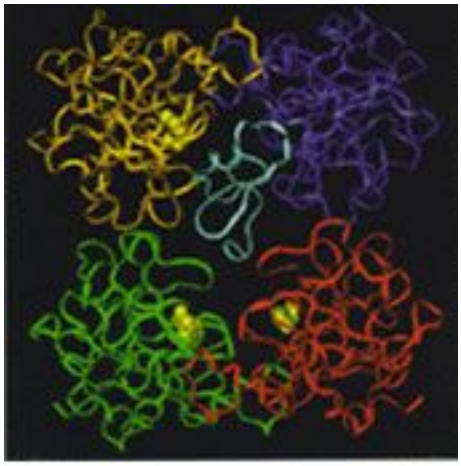
Respiratory diseases can arise from a number of causes, including inhalation of toxic agents, accidents, and harmful lifestyles, such as smoking. Infections, genetic factors, and anything else that affects lung development, either directly or indirectly, can cause respiratory symptoms.

Asthma

Asthma affects more than 5% of the population of the US, including children. It is a chronic inflammatory disorder of the airways characterized by coughing, shortness of breath, and chest tightness. A variety of "triggers" may initiate or worsen an asthma attack, including viral respiratory infections, exercise, and exposure to irritants such as tobacco smoke. The physiological symptoms of asthma are a narrowing of the airways caused by edema (fluid in the intracellular tissue space) and the influx of inflammatory cells into the walls of the airways.

Asthma is a what is known as a "complex" heritable disease. This means that there are a number of genes that contribute toward a person's susceptibility to a disease, and in the case of asthma, chromosomes 5, 6, 11, 14, and 12 have all been implicated. The relative roles of these genes in asthma predisposition are not clear, but one of the most promising sites for investigation is on chromosome 5. Although a gene for asthma from this site has not yet been specifically identified, it is known that this region is rich in genes coding for key molecules in the inflammatory response seen in asthma, including cytokines, growth factors, and growth factor receptors.

The search for specific asthma genes is ongoing. Assisting in this international human effort are model organisms such as mice, which have similar chromosomal architecture to our chromosome 5 site on their chromosomes 11, 13, and 18. Further study of the genes in these areas (and others) of the human genome will implicate specific genes involved in asthma and perhaps also suggest related biological pathways that play a role in the pathogenesis of asthma.



Tryptase is an enzyme found specifically in mast cells, a type of white blood cells important for fighting infection. It may have a role in casuing asthma and other inflammatory disorders. [Reproduced from Pereira, P.J.B. et al. (1998) Nature 392, 30-311, with permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=asthma] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=asthma&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4501969&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=asthma%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=asthma] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600807] catalog of human genes and disorders

Websites

Global initiative for asthma [www.ginasthma.com:80/] a project conducted in collaboration with the National Heart, Blood and Lung Institute, NIH, and the World Health Organization

National Heart, Blood and Lung Institute [www.nhlbi.nih.gov/health/public/lung/index.htm#asthma] information on asthma

MEDLINE*plus* [www.nlm.nih.gov/medlineplus/asthma.html] links on asthma compiled by the National Library of Medicine

Cystic Fibrosis

Cystic fibrosis (CF) is the most common fatal genetic disease in the US today. It causes the body to produce a thick, sticky mucus that clogs the lungs, leading to infection, and blocks the pancreas, stopping digestive enzymes from reaching the intestines where they are required to digest food.

CF is caused by a defective gene, which codes for a sodium and chloride (salt) transporter found on the surface of the epithelial cells that line the lungs and other organs. Several hundred mutations have been found in this gene, all of which result in defective transport of sodium and chloride by epithelial cells. The severity of the disease symptoms of CF is directly related to the characteristic effects of the particular mutation(s) that have been inherited by the sufferer.

CF research has accelerated sharply since the discovery of CFTR in 1989. In 1990, scientists successfully cloned the normal gene and added it to CF cells in the laboratory, which corrected the defective sodium chloride transport mechanism. This technique—gene therapy—was then tried on a limited number of CF patients. However this treatment may not be as successful as originally hoped. Further research will be required before gene therapy, and other experimental treatments, prove useful in combating CF.

Building mouse models of human disease. Expression of a human cystic fibrosis (CFTR) gene in the gut of a mouse. A human anti-sense probe was used to show human CFTR expressed in the mouse duodenem. [Reproduced with permission from Manson, A.L. et al. (1997) EMBO J. 16, 4238-4249.]

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Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=6995996&org=1] related sequences in different organisms

The literature

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Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=cystic%20fibrosis] online books section

OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=cystic%20fibrosis] catalog of human genes and disorders

Websites

Fact sheet [www.nhlbi.nih.gov/health/public/lung/other/cystfib.htm] from the National Heart, Lung and Blood Institute, NIH

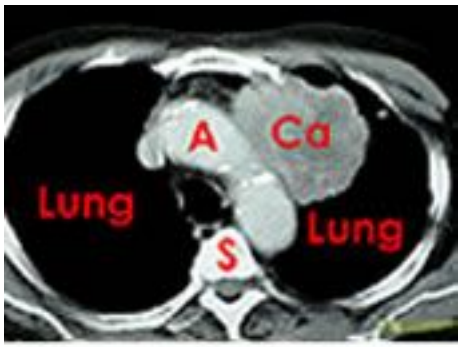
The Cystic Fibrosis Foundation [www.cff.org/] information and links

Lung Carcinoma, Small Cell

In the US, lung cancer is the most common cause of cancer deaths among both men and women. In fact, North Americans have the highest rates of lung cancer in the world. In 1997, some 178,100 new cases were diagnosed, and roughly 160,400 deaths occurred from the disease. Sadly, the 5-year survival rate for persons with lung cancer is only 14%. Since the 1940s, the increase in lung cancer mortality by gender has followed historic patterns of smoking, with a 20-year time lag. About 90% of male lung cancer deaths and 80% of female lung cancer deaths are attributable to cigarette smoking. Although smoking is by far the major risk factor for lung cancer, certain industrial substances, such as asbestos, and environmental factors can contribute.

Small cell lung carcinoma is distinctive from other kinds of lung cancer (metastases are already present at the time of discovery) and accounts for approximately 110,000 cancer diagnoses annually. A deletion of part of chromosome 3 was first observed in 1982 in small cell lung carcinoma cell lines.

As with other cancers, mutations in a variety of molecules (oncogenes and tumor-suppressor genes) that control cell growth and division are observed, and no one mutation is likely to result in cancerous growth. Basic research into the function of these molecules—how and when they play their role—should help the fight against lung, and other, cancers and give clues to find appropriate therapies.



CT scan showing lung cancer. [Image credit: Pat Connelly, Miami Valley Hospital, Dayton, OH, USA.]

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OMIM [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=lung+cancer] catalog of human genes and disorders

Websites

CancerNet [cancernet.nci.nih.gov/] from the National Cancer Institute, NIH

American Cancer Society [www.cancer.org] research and patient support

Oncolink [oncolink.upenn.edu/] comprehensive cancer information from the University of Pennsylvania